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A PROCESS FOR THE PRODUCTION OF BENZYL DL-MANDELATE

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1. Title: A process for the production of benzyl dl-mandelate

2. Patent Claims

1. A process for the production of benzyl dl-mandelate, characterized by reacting a water-soluble dl-mandelic acid salt with benzyl chloride in the presence of a quaternary salt type cationic surfactant using water as reaction medium.

2. A process for production in accordance with Claim 1, wherein the water-soluble dl-mandelic acid salt is at least one species selected from sodium dl-mandelate, ammonium dl-mandelate and potassium dl-mandelate.

3. A process for production in accordance with Claim 1, wherein the quaternary salt type cationic surfactant is at least one species selected from quaternary ammonium salt type cationic surfactant, quaternary phosphonium salt type cationic surfactant and quaternary pyridinium salt type cationic surfactant.

4. A process for production in accordance with Claim 1, wherein the water-soluble dl-mandelic acid salt is at least one species selected from sodium dl-mandelate, ammonium dl-mandelate and potassium dl-mandelate, and the quaternary salt type cationic surfactant is at least one species selected from quaternary ammonium salt type cationic surfactant, quaternary phosphonium salt type cationic surfactant and quaternary pyridinium salt type cationic surfactant.

Detailed Description of the Invention

This invention relates to a process for the production of benzyl dl-mandelate.

Benzyl dl-mandelate is a white solid of mp. 93°C, and is a useful substance as a drug (urethral antibacterial agent) or as a drug intermediate.

This substance was synthesised for the first time in 1923, using a process wherein sodium dl-mandelate is reacted with benzyl hydrochloride, however, there are disadvantages with this process in that both starting materials react together with difficulty, and in addition, even the produced aforesaid ester is subject to decomposition by hydrochloric acid formed by decomposition of the starting material benzyl chloride, and the synthesis yield thereby depressed.

Accordingly, in 1954, there was developed a process to synthesise the said ester by the reaction of dl-mandelic acid with benzyl alcohol, and since then this process has formed the

main stream synthesis method of the said ester to date. However, the starting material of this process benzyl alcohol is generally produced from benzyl chloride which is the starting material of the said prior art process, and is expensive costing 4-5 times more than benzyl chloride. Therefore, this process is not an excellent process for production of the said ester from the aspect of the costs of the starting materials.

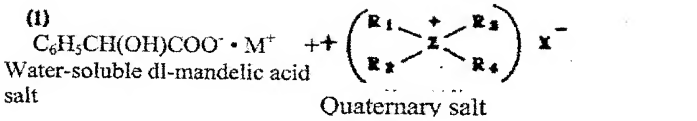
Moreover, there is a process in the literature producing the said ester by the reaction of barium dl-mandelate with benzyl sulfonic acid, however, it cannot be said to be a practical process since there are disadvantages in that the decomposition of the said ester is readily induced, and in addition the starting material benzyl sulfonic acid is hard to obtain and is expensive.

Therefore the development is desired of a process to produce benzyl dl-mandelate with good efficiency using inexpensive starting material.

This invention was conceived in response to the aforesaid demand, and is a process wherein a water-soluble dl-mandelic acid salt is reacted with benzyl chloride in the presence of cationic surfactant (particularly a quaternary salt type) using water as reaction medium. In this reaction, this inventor believes that a quaternary salt type cationic surfactant acts as a catalyst.

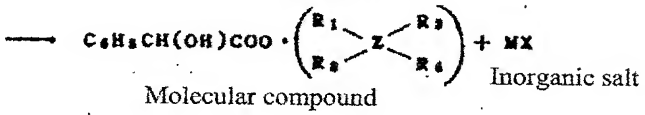
In other words, this inventor believes that; firstly in step (1), a quaternary salt type cationic surfactant forms a molecular compound by electrically combining with dl-mandelic acid radical (anion) in water as shown the following equation. Because this molecular compound is lipophilic, it mixes uniformly with the lipophilic benzyl chloride, and, in step (2), the benzyl chloride and dl-mandelic acid react in this condition, and as a result form benzyl dl-mandelate, and the quaternary salt thereby released from the molecular compound, bonds electrically once again with another dl-mandelic acid radical in water in step (1). In this way, the aforesaid procedures are repeated many times, and the benzyl dl-mandelate is thereby gradually produced.

(1)



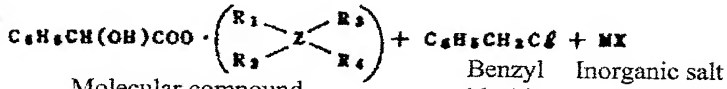
$C_6H_5CH(OH)COO^- \cdot M^+$ ++ Quaternary salt

Water-soluble dl-mandelic acid salt

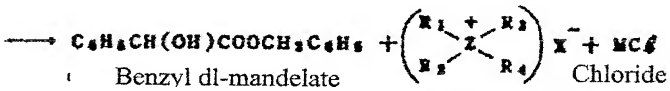


Molecular compound Inorganic salt

(2)



Molecular compound Benzyl chloride Inorganic salt



Benzyl dl-mandelate Quaternary salt Chloride

+)

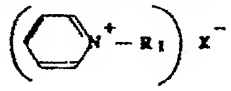
(1) + (2) $C_6H_5CH(OH)COOM$ + $C_6H_5CH_2Cl$

Water-soluble dl-mandelic salt Benzyl chloride

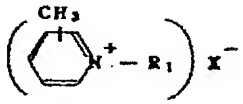
⟶ $C_6H_5CH(OH)COOH2C6H5$ + MCl

Benzyl dl-mandelate Chloride

wherein, the said quaternary salt may be modified to



or



Wherein, each symbol has the following definitions;

Z: nitrogen atom or phosphorus atom.

R_1, R_2, R_3, R_4: alkyl, aralkyl, cycloalkyl or aryl group.

M: alkali metal or ammonium group.

X: halogen or acid radical.

The aforesaid theoretical assumption of this inventor was demonstrated to be correct by a number of experiments carried out as described later. This invention was completed on this basis.

The process of this invention has the following advantages compared to the prior art process. Namely, in productions using the prior art process, arduous recrystallisation, solvent extraction and the like is required in order to eliminate the said inorganic salt which

contaminates the said ester, but on the other hand in accordance with the process of this invention, because water is used as reaction medium, the co-produced inorganic acid dissolves away in this water, and therefore recrystallisation and solvent extraction steps for eliminating the said inorganic acid can be omitted, and moreover, even dl-mandelic acid containing inorganic acid salt can be used as starting material, and substantial advantages are demonstrated.

Examples of water-soluble dl-mandelic acid salt used in this invention includes sodium dl-mandelate, ammonium dl-mandelate and potassium dl-mandelate. These salts can be readily produced by causing caustic alkali (or alkaline carbonate) or ammonia to act on dl-mandelic acid suspended in water to form an aqueous solution of the dl-mandelic acid salt, and this can be used in the process of this invention as an aqueous solution itself without further treatment. Also the aforesaid solid salt can be made into and used in the form of the aqueous solution. Moreover, as long as use is made in the form of an aqueous solution, dl-mandelic acid salts other than the aforesaid salt may be used.

Cationic surfactants in accordance with this invention are quaternary salt type cationic surfactants. More particularly, cationic surfactants of the quaternary ammonium salt type, quaternary phosphonium salt type and quaternary pyridinium salt type as represented in the aforesaid reaction equations, may be used. For example stearyl trimethylammonium chloride, distearyl dimethylammonium chloride, benzyl trimethylammonium chloride, tetrabutylammonium hydrodien(sic) sulfate, lauryl trimethylammonium chloride, tetramethylammonium chloride, benzyl triethylammonium chloride, benzyl tributylammonium chloride, tetrabutylammonium bromide, trioctylmethylammonium chloride, tetrabutyl phosphonium bromide, tetrabutyl phosphonium chloride, benzyl triphenyl phosphonium chloride, N-laurylpyridinium chloride, N-laurylpicolinium chloride, N-benzylpicolinium chloride and the like may be proposed; however there is no restriction to these as long as a quaternary salt type cationic surfactant is used.

The quantity of cationic surfactant used may be the catalytic quantity. Generally, 0.08-0.005 mole is used per mole of mandelic acid salt.

The quantity of water used as reaction medium is ideally a quantity of 100-250% with respect to the calculated amount of mandelic acid contained in the starting material.
As far as the quantity of benzyl chloride used is concerned, theoretically the reaction with the water-soluble dl-mandelic acid salt is an equimolar one, but preferably slightly less than the amount of water-soluble dl-mandelic acid salt is preferably used, because the said acid is

readily subject to hydrolysis. Accordingly, about 0.8-0.9 mole of benzyl chloride is used per mole of the said salt.

Moreover, the reaction temperature is 70-110°C and a reaction time of 4-15 hours is required.

Hereinafter this invention will be explained in greater detail by reference to Examples and Comparative Examples, but it should be understood however, that as long as there is no deviation from the scope of this invention, this invention is not limited by the following Examples.

Example 1

To 80 ml water were added 46.7 g (0.307 mol) dl-mandelic acid and 16.6 ml sodium hydroxide solution (73.9 vol% product) to make a uniform solution, and thereafter thereto were added 7.4 g (0.023 mol) tetrabutylammonium bromide and 35 g (0.276 mol) benzyl chloride, and the mixture was stirred while maintaining the temperature at about 100°C for 10 hours. Thereafter the obtained reaction liquor was left to stand, the water insoluble fraction 84.5 g was subjected to liquid separation, and dissolved in 40 ml methanol at 60°C and thereafter cooled to about 20°C. The thereby formed white crystalline precipitate was filtered and dried, and benzyl dl-mandelate of mp. 93°C was thereby obtained in an amount of 49 g representing a yield of 73.2% (theoretical value).

Moreover, the water-soluble fraction formed when the reaction liquor was left to stand, was left at room temperature overnight, whereupon the acidic sodium salt of dl-mandelic acid (calculated dried reduced value 3 g) was precipitated, and this was isolated and recovered.

Example 2

The same procedures as in Example 1 were repeated but with the use of 17.2 g potassium hydroxide instead of 16.6 ml sodium hydroxide solution (73.9 vol% product), and thereby benzyl dl-mandelate was obtained in an amount of 50.2 g representing a yield of 75.0% (theoretical value).

Example 3

Mandelic acid nitrile was hydrolysed with hydrochloric acid and the thereby obtained 110 g solution (aqueous solution including 46.7 g dl-mandelic acid, 16.1 g ammonium chloride and some hydrochloric acid) was neutralised with concentrated ammonia water till the pH became pH7.0. Thereafter, thereto were added 7.4 g tetrabutylammonium bromide and 35 g benzyl chloride, and the mixture was stirred while maintaining the temperature at about 90-95°C for 9 hours.

Thereafter the obtained reaction liquor was subjected to the same procedures as in Example 1 and liquid separation and methanol treatment were carried out, and benzyl dl-mandelate was obtained in an amount of 46.8 g representing a yield of 69.9% (theoretical value).

Examples 4-18

The same procedures as in Example 1 were repeated using the following cationic surfactant in the amounts described in the Table instead of 7.4 g tetrabutylammonium bromide, and thereby the quantities of benzyl dl-mandelate shown in the Table were obtained.

Ex. No.	Used surfactant		Obtained benzyl dl-mandelate	
	Name	Quantity used (g)	Quantity obtained (g)	Yield/ theoretical value (%)
4	tetramethylammonium chloride	1.3	43.4	64.9
5	benzyl trimethylammonium chloride	2.2	40.1	59.9
6	benzyl tributylammonium chloride	3.6	38.9	58.1
7	tetrabutylammonium hydrogen sulfate	3.9	40.1	59.9
8	trioctylmethylammonium chloride	4.7	41.2	61.6
9	tetrabutyl phosphonium bromide	3.9	38.9	58.1
10	tetrabutyl phosphonium chloride	3.4	35.6	53.2
11	benzyl triphenyl phosphonium chloride	4.7	38.9	58.1
12	lauryl trimethylammonium chloride	3.1	40.1	59.9
13	stearyl trimethylammonium chloride	4.0	41.2	61.6
14	distearyl dimethylammonium chloride	4.0	41.2	59.9
15	benzyl triethylammonium chloride	2.6	46.8	69.9
16	N-laurylpyridinium chloride	3.4	35.6	53.2
17	N-laurylpicolinium chloride	3.5	38.9	58.1
18	N-benzylpicolinium chloride	2.3	40.1	59.9

Comparative Example 1

Benzyl dl-mandelate was obtained in an amount of 3.3 g representing a yield of 5% (theoretical value) by repeating the same procedures as in Example 1 but without using any quaternary salt type cationic surfactant whatsoever.

Comparative Example 2

A mixture of 53.5 g (0.307 mole) dl-mandelic acid sodium salt and 35 g (0.276 mole) benzyl chloride was stirred while heating at about 179°C for 10 hours, and thereafter the unreacted benzyl chloride was eliminated by distillation. To the thereby obtained residue was added 80 ml methanol and the methanol-soluble components were extracted. The methanol was eliminated from the obtained liquid extract, and 6.7 g of benzyl dl-mandelate was obtained (yield 10% / theoretical value).

As may be understood from the aforesaid explanation and Examples, this invention is a novel process for the production of benzyl dl-mandelate using quaternary salt type cationic surfactant as reaction catalyst, water as reaction medium and a water-soluble dl-mandelic acid salt and benzyl chloride as starting materials; and compared to the said prior art production processes, the procedures of the process for production of this invention can be said not only to be simple but also economical.

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